REMARKS

The present invention relates to water soluble or dispersible porous bodies and to methods of producing such porous bodies.

Independent Claim 1 is directed to water soluble porous bodies which are a water-soluble lattice containing a water-insoluble "payload" material, i.e., a water-insoluble material is incorporated into said lattice to be dispersed when the water-soluble porous body dissolves. This is described at page 2, lines 16 to 27 and at page 6, lines 21 to 23 of the Specification.

Independent Claim 11 is directed to a method for preparing water soluble porous bodies, starting with a water soluble polymeric material other than a surfactant. Claim 11 has been amended to specify that the emulsion is comprised of a continuous phase and a discontinuos oil phase, thereby providing proper antecendent basis for claims 18 and 19. Support for this subject matter may be found in the Specification, at page 6, for example. Care has been taken not to introduce any new matter.

The porous bodies of the present invention facilitate dispersion and, in many cases, enables hydrophobic materials to be dispersed more effectively than previously.

Claims Are Not Obvious under 35 USC § 103

Claims 1, 4-8, 10-11 and 13-21 were rejected as obvious over Wu, et al., as evidenced by Steiner, et al., and Pruss, et al. Also, Claims 1, 4-8 and 10-17 were rejected as obvious over Pruss, et al. Claim 22 had been previously canceled. Applicants respectfully traverse.

Regarding the product claims, Applicants respectfully submit that it is improper to refer to the "method of manufacture" description in Wu, et al., to arrive at the percentages of components in the Office Action (see columns 3 to 7). Instead, as claim 1 is a product claim, reference should be to the description of the percentages of the components in the powder in column 8 (lines 20-42), where the ranges stated below are disclosed.

Wu, et al., discloses a water insoluble powder in the form of a pseudo-lattice comprising:

• about 42.5-98% of a water ***insoluble*** polymer, e.g., cellulose acetate phthalate (CAP) or cellulose acetate succinate (CAS), and

• a total emulsifier (surfactant) content of about 57.5-1.5%, and ***optionally***

• a suitable medicament/active ingredient which exhibits low solubility in water

in the form of particles having an average particle size of 10-30 µm, i.e., water soluble microparticles (below 0.2 mm) – see column 8, lines 20-39 which define the powder composition itself and not the amounts of ingredients used to manufacture the powder.

This <u>water insoluble</u> powder in Wu *et al.* is suitable for film-coating medicaments. The powder can be added to water to create an aqueous, polymeric, colloidal dispersion which is suitable in cosmetic formulations (column 3, lines 5-24 - note that a "dispersion" of a non-soluble entity is formed rather than a "solution" of a soluble entity).

The Office Action *asserts* (but in Applicants' view does not provide conclusive evidence) that two of the examples of a water insoluble polymer given in the specification, cellulose acetate phthalate (CAP) and cellulose acetate succinate (CAS), are in fact water ***soluble***. The Office Action refers to Steiner *et al.* to back up this assertion: column 2, lines 42-44 state that "with respect to water soluble derivatives of cellulose acetate, cellulose acetate phthalate and cellulose acetate succinate are exemplary of water soluble derivatives". However, when viewed as a whole and taken within context, the remainder of the paragraph in column 2 states that "these derivatives are pH sensitive and when dissolving in water, the water must be maintained as a mildly acidic to basic medium, having a pH of from about to 6.0 to 9.0". Indeed both CAP and CAS are enteric polymers; see:

http://en.wikipedia.org/wiki/Enteric_coating (copy enclosed)

http://www.enerex.ca/articles/enteric_coating.htm (copy enclosed)

Attention is called to the the wording in Wu *et al.* which lists quite specifically the types of water insoluble polymers that can be used:

1. ***pH-dependent acidic enteric*** cellulosic polymers, e.g. CAP and CAS
2. ***neutral*** cellulosic esters
3. ***pH-dependent basic*** cellulosic polymers
4. ***pH-dependent basic*** polyvinylpyridine and polystyrene derivatives
5. maleic anhydride copolymers
6. acrylic/acrylate copolymers and acrylic esters
7. other polymers, e.g. biodegradable polymers, which meet the definition of water insoluble polymers

Additionally, Applicants respectfully submit that:

- CAP dissolves into buffer solution (pH > 6), into acetone, but <u>not</u> into ethanol and water;
- CAS slowly dissolves into buffer solution (pH 5.5 ~ 7.5), easily dissolves into acetone, but does <u>not</u> dissolve into ethanol and water.

Furthermore, it is stated in Wu *et al.* in column 6, line 60 that the polymer solution phase (in Step I of the method of manufacture) is an organic phase (i.e. not aqueous), which supports all of the above in the fact that <u>CAP and CAS are water insoluble</u>.

Regarding the method of manufacture described in Wu *et al.*, this is <u>not</u> an emulsion-templating process, as defined in the present claims. The method described in Wu *et al.* involves a series of processing steps, which together form a quite complicated and lengthy process (described at column 3, line 37 to column 4, line 13), beginning with formation of a water-in-oil emulsion using comminuting force (the oil being an organic phase containing the water insoluble polymer), followed by addition of more water to achieve a phase inversion resulting in an oil-in-water emulsion. There follows three optional (but presumably compulsory if a powder is desired) processing steps of:

(1) reducing the size of the <u>water insoluble polymer particles</u> (to a range of 0.1-0.8 μm) to ***micro***particles (not nanoparticles) – by use of any particle size reduction means, e.g. a Microfluidizer (column 8, lines 1-6);

(2) removing the organic solvent from the emulsion to form an "aqueous colloidal dispersion of polymer" – by any means known in the art, e.g. use of distillation methodology preferably under reduced pressure (column 8, lines 12-16);

(3) drying the aqueous colloidal dispersion to form a water-dispersible powder - by any drying means known in the art, e.g. spray-drying or freeze-drying (column 8, lines 17-19).

Thus the water dispersible powder of Wu *et al.* is produced *via* a precipitation route that produces a colloidal suspension of "lumps" of water insoluble polymer that is then dried; the organic solvent having already been removed. This is <u>not</u> emulsion-templating, in which it is ***essential*** to maintain the structure of the emulsion all the way through to the final porous bodies (the pores being a direct result of the emulsion

structure) – this is achieved in the present invention by freeze-drying the emulsion itself to "lock" the porous structure into the resultant polymer/surfactant bodies.

Accordingly, the Office Action position notwithstanding, claims 1 and 11 are inventive over Wu *et al.* (as evidenced by Steiner *et al.*) because there is no disclosure in Wu *et al.* of porous bodies containing ***less than 10 %*** by weight of a water soluble polymer other than a surfactant and of the body having an intrusion volume of at least about 3ml/g, or of said porous bodies having been made by an emulsion-templating (via freeze-drying) process. Moreover, Pruss et al. fails to remedy the deficiencies of Wu and Steiner, as discussed below.

Turning to Pruss *et al.*, a fast melt dosage form comprising at least one active agent and at least one pharmaceutically acceptable water-soluble excipient are disclosed. The active agent can be nanoparticulate in size and poorly soluble in at least one aqueous or non-aqueous liquid dispersion medium – see paragraph [0053] – i.e. it is added already in the form of nanoparticles, rather than nanoparticles resulting from the method disclosed therein.

The pharmaceutically acceptable excipient can be water soluble or water dispersible, and may be, e.g. a natural polymer or a synthetic polymer – see paragraph [0086]. The excipient can be present in the final formulation in an amount of from 99.9-0.1 % (w/w) based on the total weight of the dry composition.

Paragraph [0088] provides a list of other pharmaceutically acceptable excipients that may be included in the composition, including a wetting agent Paragraph [0100] describes the percentages of some of these additional excipients, but none is provided for the wetting agent.

Paragraphs [0104] to [0112] describe the methods by which the composition, prior to being made into a tablet, can be produced. The Office Action refers specifically

to paragraph [0111] which discusses lyophilization and references Erbeia. However there is no disclosure in Pruss *et al.* of forming the composition *via* an emulsion-templating process – paragraph [0104] states that the active agent and pharmaceutically acceptable excipient can be "combined", while paragraph [0107] states that the ingredients can be "blended". Blending of the ingredients can be achieved by use of any commercially available blending vessel (paragraph [0110]) ***or*** by lyophilizing (i.e. freeze-drying) a ***dispersion*** of the ingredients (paragraph [0111]) ***or*** by granulating in a fluidized bed an admixture of the ingredients (paragraph [0112]).

There is <u>no</u> disclosure of forming an emulsion containing the active agent and/or the excipient, or of a subsequent emulsion-templating process to form porous bodies of the excipient having the active agent incorporated therein.

Accordingly, independent claims 1 and 11 are also inventive over Pruss *et al.*, alone or in combination with Wu and Steiner, because there is no disclosure in Pruss *et al.* of a (porous) body containing 5-95 % by weight of a surfactant, or of said porous bodies having been made by an emulsion-templating (via freeze-drying) process. Although a wetting agent is mentioned, no percentage weight is given.

In view of the disclosures in each of Wu *et al.* and Pruss *et al.*, there would be no benefit to the skilled person in combining these documents. Modifying either of the teachings of Wu *et al.* or Pruss *et al.* with the other would <u>not</u> lead to the present invention because neither discloses or even suggests the use of an emulsion-templating method. Furthermore, neither teaches porous bodies comprised of a water soluble polymer and a surfactant in the weight percentages taught by claim 1.

For all of the above reasons, it is believed that all the claims are non-obvious over the documents cited in the Office Action, whether alone or in combination.

CONCLUSION

Reconsideration of the rejection is respectfully requested in view of the above remarks.

It is respectfully requested that the application be allowed to issue.

If a telephone conversation would be of assistance, Applicant's undersigned attorney invites the Examiner to telephone at the number provided.

Respectfully submitted,

/Ellen Plotkin/

Ellen Plotkin
Attorney for Applicant(s)
Reg. No. 36,636

(201) 894-2253

Enteric coating

From Wikipedia, the free encyclopedia

An **enteric coating** is a barrier applied to oral medication that controls the location in the digestive system where it is absorbed. *Enteric* refers to the small intestine, therefore enteric coatings prevent release of medication before it reaches the small intestine.

Most enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a less acidic (relatively more basic) pH. For example, they will not dissolve in the acidic juices of the stomach (pH ~3), but they will in the higher pH (above pH 5.5) environment present in the small intestine. Materials used for enteric coatings include fatty acids, waxes, shellac and plastics, plant fibers.

Drugs that have an irritant effect on the stomach, such as aspirin, can be coated with a substance that will only dissolve in the small intestine. Similarly, certain groups of azoles (esomeprazole, omeprazole, pantoprazole and all grouped azoles) are acid-unstable. For such types of drugs, enteric coating added to the formulation tends to avoid the stomach's acidic exposure, delivering them instead to a basic pH environment (intestine's pH 5.5 and above) where they do not degrade, and give their desired action.

Recently, some companies have begun to utilize enteric coatings on fish oil (omega 3 fatty acids) supplements. The coating prevents the fish oil capsules from being digested in the stomach, which has been known to cause a fishy reflux (fish burps).

Sometimes the abbreviation "EC" is added beside the name of the drug to indicate that it is enteric coated.

Composition of coatings

- Cellulose acetate phthalate (CAP)
- methyl acrylate-methacrylic acid copolymers
- cellulose acetate succinate
- hydroxy propyl methyl cellulose phthalate
- hydroxy propyl methyl cellulose acetate succinate (hypromellose acetate succinate)
- polyvinyl acetate phthalate (PVAP)
- methyl methacrylate-methacrylic acid copolymers
- Sodium alginate and stearic acid

See also

- Phthalates

External links

Definition of "enteric coating" in the free dictionary website (http://medical-dictionary.thefreedictionary.com/coating,+enteric)

Retrieved from "http://en.wikipedia.org/wiki/Enteric_coating"
Categories: Pharmacology | Coatings | Polymers

- This page was last modified on 3 March 2010 at 18:36.

Enteric Coating

Cellulose Acetate Phthalate is used as an enteric coating on capsules or tablets so they don't dissolve until they reach the small intestine. Enteric coatings are selectively insoluble substances - they won't dissolve in the acidic juices of the stomach, but they will dissolve in the higher pH (above pH 5.5) of the small intestine. Serrapeptase™ Rx capsules are enteric coated because the effectiveness of the drug will be reduced by stomach acids or enzymes if left unprotected.

Cellulose Acetate Phthalate

1. Nonproprietary Names

- BP: Cellacefate
- JP: Cellulose acetate phthalate
- PhEur: Cellulosi acetas phthalas
- USPNF: Cellacefate

2. Synonyms

- Acetyl phthalyl cellulose; *Aquacoat cPD*; CAP; cellacephate; cellulose acetate benzene-1,2-dicarboxylate; cellulose acetate hydrogen 1,2-benzenedicarboxylate; cellulose acetate hydrogen phthalate; cellulose acetate monophthalate; cellulose acetophthalate; cellulose acetylphthalate.

3. Chemical Name and CAS Registry Number

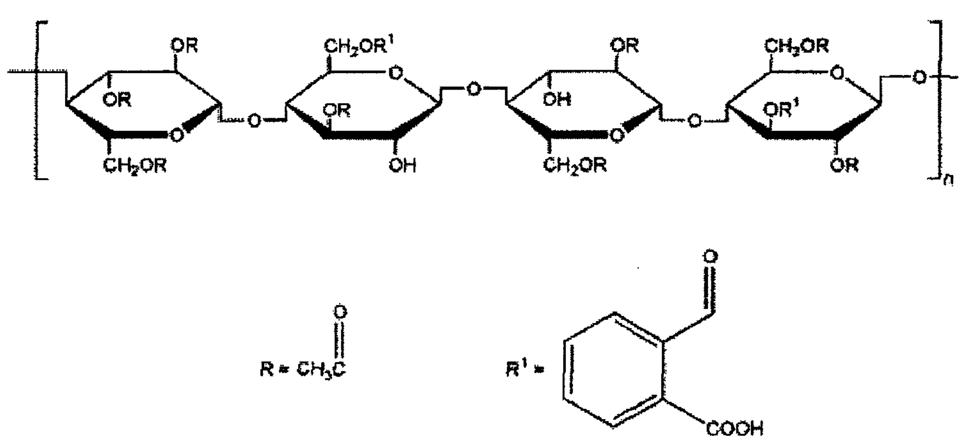
- Cellulose, acetate, 1,2-benzenedicarboxylate [9004-38-0]

4. Empirical Formula and Molecular Weight

- Cellulose acetate phthalate is a cellulose in which about half the hydroxyl groups are acetylated, and about a quarter are esterified with one of two acid groups being phthalic acid, where the remaining acid group is free. *See* Section 5.

5. Structural Formula

The PhEur 2002 (Suppl. 4.3) and USPNF 21 describe cellulose acetate phthalate as a reaction product of phthalic anhydride and a partial acetate ester of cellulose containing 21.5-26.0% of acetyl (C_2H_3O) groups, and 30.0-36.0% of phthalyl(*o* -carboxybenzoyl, $C_8H_5O_3$) groups.



6. Functional Category

- Coating agent.

7. Applications in Pharmaceutical Formulation or Technology

- Cellulose acetate phthalate (CAP) is used as an enteric film coating material, or as a matrix binder for tablets and capsules. 1 - 8 Such coatings resist prolonged contact with the strongly acidic gastric fluid, but dissolve in the mildly acidic or neutral intestinal environment.
- Cellulose acetate phthalate is commonly applied to solid-dosage forms either by coating from organic or aqueous solvent systems or by direct compression. Concentrations generally used are 0.5-9.0% of the core weight. The addition of plasticizers improves the water resistance of this coating material, and formulations using such plasticizers are more effective than when cellulose acetate phthalate is used alone.
- Cellulose acetate phthalate is compatible with many plasticizers, including acetylated monoglyceride; butyl phthalybutyl glycolate; dibutyl tartrate; diethyl phthalate; dimethyl phthalate; ethyl phthalylethyl glycolate; glycerin; propylene glycol; triacetin; triacetin citrate; and tripropionin. It is also used in combination with other coating agents such as ethyl cellulose, in drug controlled-release preparations.
- Therapeutically, cellulose acetate phthalate has recently been reported to exhibit experimental microbicidal activity against sexually transmitted disease pathogens, such as the HIV-1 retrovirus. 9, 10

8. Description

- Cellulose acetate phthalate is a hygroscopic, white to off-white, free-flowing powder, granule, or flake. It is tasteless and odorless, or might have a slight odor of acetic acid.

9. Pharmacopeial Specifications

- *See* Table I.

10. Typical Properties

- Density (bulk): 0.260 g/cm 3
- Density (tapped): 0.266 g/cm 3
- Melting point: 192°C. Glass transition temperature is 160-170°C. 11
- Moisture content: 2.2%. Cellulose acetate phthalate is hygroscopic and precautions are necessary to avoid excessive absorption of moisture. 12 *See also* Figure 1.
- Solubility: practically insoluble in water, alcohols, and chlorinated and non-chlorinated hydrocarbons. Soluble in a number of ketones, esters, ether alcohols, cyclic ethers and in certain solvent mixtures. It can be soluble in certain buffered aqueous solutions as low as pH 6.0. Cellulose acetate phthalate has a solubility of =10% w/w in a wide range of solvents and solvent mixtures; Table II and Table III.
- Viscosity (dynamic): a 15% w/w solution in acetone with a moisture content of 0.4% has a viscosity of 50-90 mPa s. This is a good coating solution with a honey-like consistency, but the viscosity is influenced by the purity of the solvent.

11. Stability and Storage Conditions

- Slow hydrolysis of cellulose acetate phthalate will occur under prolonged adverse conditions such as high temperatures and high humidity, with a resultant increase in free acid content, viscosity, and odor of acetic acid. However, cellulose acetate phthalate is stable if stored in a well-closed container in a cool, dry place.

12. Incompatibilities

- Cellulose acetate phthalate is incompatible with ferrous sulfate, ferric chloride, silver nitrate, sodium citrate, aluminum sulfate, calcium chloride, mercuric chloride, barium nitrate, basic lead

acetate, and strong oxidizing agents such as strong alkalis and acids.

13. Method of Manufacture

- Cellulose acetate phthalate is produced by reacting the partial acetate ester of cellulose with phthalic anhydride in the presence of a tertiary organic base such as pyridine, or a strong acid such as sulfuric acid.

14. Safety

- Cellulose acetate phthalate is widely used in oral pharmaceutical products and is generally regarded as a nontoxic material, free of adverse effects.
- Results of long-term feeding in rats and dogs have indicated a low oral toxicity. Rats survived daily feedings of up to 30% in the diet for up to 1 year without showing a depression in growth. Dogs fed 16 g daily in the diet for 1 year remained normal.

15. Handling Precautions

- Observe normal precautions appropriate to the circumstances and quantity of material handled. Cellulose acetate phthalate may be irritant to the eyes, mucous membranes, and upper respiratory tract. Eye protection and gloves are recommended. Cellulose acetate phthalate should be handled in a well-ventilated environment; use of a respirator is recommended when handling large quantities.

16. Regulatory Status

- Included in the FDA Inactive Ingredients Guide (oral tablets). Included in non-parenteral medicines licensed in the UK .

17. Related Substances

- Cellulose acetate; hypromellose phthalate; polyvinyl acetate phthalate.

18. Comments

- Any plasticizers that are used with cellulose acetate phthalate to improve performance should be chosen on the basis of experimental evidence. The same plasticizer used in a different tablet base coating may not yield a satisfactory product.
- In using mixed solvents, it is important to dissolve the cellulose acetate phthalate in the solvent with the greater dissolving power, and then to add the second solvent. Cellulose acetate phthalate should always be added to the solvent, not the reverse.
- Cellulose acetate phthalate films are permeable to certain ionic substances, such as potassium iodide and ammonium chloride. In such cases, an appropriate sealer sub-coat should be used.
- A reconstituted colloidal dispersion of latex particles rather than solvent solution coating material of cellulose acetate phthalate is also available. This white, water-insoluble powder is composed of solid or semisolid sub-micrometer-sized polymer spheres with an average particle size of 0.2 µm. A typical coating system made from this latex powder is a 10-30% solid-content aqueous dispersion with a viscosity in the 50-100 mPa s range.

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21. Author

- RW Fengl.

22. Date of Revision

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